

Application No. 09/242,772
Paper Dated September 8, 2003
In reply to USPTO correspondence dated 05/05/2003 and 8/11/03
Attorney Docket No. 3374-990278

AMENDMENTS TO THE CLAIMS

Following is the list of claims and their status:

1-27 (Canceled)

28. (Currently Amended): A An isolated nucleic acid in isolated form, comprising a sequence encoding a wherein the nucleic acid encodes a protein which is homologous to the protein encoded by the PLAG1 (pleomorphic adenoma gene 1) protein gene, wherein the amino acid eDNA sequence corresponding to said of the PLAG1 gene protein is the sequence translated from the nucleic acid sequence as represented in SEQ ID NO: 116 starting with the ATG at position 481 to 483 of said nucleic acid sequence, or a fragment thereof which can be used to diagnose cells having a non-physiological proliferative capacity depicted in figure 4A (SEQ ID NO: 116), and wherein a protein encoded by the nucleic acid comprises a polypeptide sequence which is at least 75% identical to the polypeptide sequence encoded by PLAG1 in the region from zinc fingers 4 to 7 as represented in SEQ ID NOS: 120 to 123, or a complementary or antisense version of the nucleic acid.

29. (Currently Amended): The nucleic acid as claimed in claim 47-28, comprising the nucleotide sequence of the *PLAG1* gene as depicted in figure 4A (SEQ ID NO: 116), or a complementary or antisense version of the nucleic acid.

30-31 (Canceled)

32. (Previously Presented): The nucleic acid as claimed in claim 47 wherein the nucleic acid is labeled.

33. (Currently Amended): A macromolecule comprising a nucleic acid in isolated form, comprising a sequence encoding a fusion of at least two of an oligonucleotide, a polynucleotide and a gene, wherein at least a first one of said oligonucleotide, polynucleotide or gene comprises a nucleotide sequence of at least one exon consisting of the PLAG1 (pleomorphic adenoma gene 1) gene, and protein, wherein the

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amino acid sequence of the PLAG1 [gene] protein is the sequence translated from the nucleic acid sequence as represented in SEQ ID NO: 116 starting with the ATG at position 481 to 483 of said nucleic acid sequence, or a fragment thereof which can be used to diagnose cells having a non-physiological proliferative capacity, at least a second one of said oligonucleotide, polynucleotide or gene comprises at least one exon of the CTNNB1 (β -catenin) gene, or complementary or antisense versions of the nucleotide sequence.

34. (Previously Presented): The macromolecule as claimed in claim 33, wherein the nucleic acid is selected from the group consisting of:

- a) a transcript corresponding to the nucleic acid;
- b) cDNA corresponding to the nucleic acid; and
- c) sense or antisense DNA corresponding to the nucleic acid.

35. (Previously Presented): The macromolecule as claimed in claim 34, wherein the nucleic acid is labeled.

36. (Previously Presented): A diagnostic kit comprising one of the labeled nucleic acid as claimed in claim 26 and a labeled macromolecule derivative of the nucleic acid and one or more diagnostic reagents.

37. (Previously Presented): The kit as claimed in claim 36, wherein the kit comprises labeled T-gene specific and tail specific PLR primers.

38. (Previously Presented): The kit as claimed in claim 36, wherein the macromolecule is a set of labeled nucleic acid probes and the kit further comprises a restriction enzyme.

39. (Previously Presented): The kit as claimed in claim 36, wherein the macromolecule is a labeled probe for *in situ* diagnostics.

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40. (Previously Presented): An *in situ* diagnostic method for diagnosing interphase and/or metaphase cells having a non-physiological proliferative capacity, comprising the steps:

- a) designing a set of nucleotide probes based on a nucleic acid as claimed in claim 26, wherein at least one of the probes is hybridisable to a region of the aberrant gene substantially mapping at the same locus as a corresponding region of the wildtype gene and/or the same or another probe is hybridsable to a region of the aberrant gene mapping at a different locus than a corresponding region of the wildtype gene;
- b) incubating one or more interphase or metaphase chromosomes or interphase or metaphase cells having a non-physiological proliferative capacity, with the probe(s) under hybridising conditions; and
- c) visualising the hybridsation between the probe(s) and the gene.

41. (Previously Presented): A method of diagnosing cells having a non-physiological proliferative capacity, comprising the steps of:

- a) taking a biopsy of a tumor to obtain cells to be diagnosed;
- b) isolating a suitable T-gene-related macromolecule therefrom;
- c) analysing the macromolecule thus obtained by comparison with a wildtype reference molecule.

42. (Previously Presented): The method as claimed in claim 41, comprising the steps of:

- a) taking a biopsy of a tumor to obtain cells to be diagnosed;
- b) extracting total RNA thereof;
- c) preparing at least one first strand cDNA of the mRNA species in the total RNA extract, which cDNA comprises a suitable tail;
- d) performing one of a PCR and a RT-PCR using one of a PLAG gene specific primer, a tail-specific and a partner-specific/nested primer to amplify PLAG gene specific cDNA's;
- e) separating the PCR products on a gel to obtain a pattern of bands;
- f) evaluating the presence of aberrant bands by comparison to wildtype bands.

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43. (Previously Presented): The method as claimed in claim 41, comprising the steps of:

- a) taking a biopsy of a tumor to obtain cells to be diagnosed;
- b) isolating total protein therefrom;
- c) separating the total protein on a gel to obtain essentially individual bands;
- d) hybridising the bands thus obtained with antibodies directed against a part of the protein encoded by a remaining part of the T-gene and against a part of the protein encoded by a substitution part of the T-gene;
- e) visualising the antigen-antibody reactions and establishing the presence of aberrant bands by comparison with bands from wildtype proteins.

44. (Previously Presented): The method as claimed in claim 41, comprising at least some of the following steps:

- a) taking a biopsy of a tumor to obtain cells to be diagnosed;
- b) isolating total DNA therefrom;
- c) digesting the DNA with a restriction enzyme;
- d) separating the digest thus prepared on a gel to obtain a separation pattern;
- e) hybridising the separation pattern in the gel or on the blot with a labeled nucleic acid in isolated form, comprising one of an oligonucleotide, a polynucleotide and a gene having a nucleotide sequence of at least a part of a T-gene selected from the group consisting of the *PLAG* subfamily of zinc finger protein genes, the *CNNB1* gene and fusions thereof, or complementary or degenerate versions of the nucleotide sequence; and
- f) visualising the hybridisations and establishing the presence of aberrant bands by comparison to wildtype bands.

45. (Previously Presented): A method for identifying a T-gene comprising the steps of:

- a) preparing one of a probe and a primer of a nucleic acid as claimed in claim 26;
- b) isolating a gene which hybridises to the probe or primer.

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46. (Previously Presented): A method of inhibiting expression of a T-gene comprising contacting a cell with a derivative as claimed in claim 33, wherein the derivative is one of an antisense nucleic acid, a nucleic acid coding for an antisense molecule, or otherwise interferes with expression of a T-gene, and an antibody or a derivative thereof.

47. (Currently Amended): A nucleic acid in isolated form according to claim 28, wherein the nucleic acid is one of an oligonucleotide, a polynucleotide and a gene comprising a sequence of at least one exon of the PLAG1 (pleiomorphic adenoma gene 1) gene, or the complementary sequence or antisense version of the nucleic acid; wherein the amino acid sequence of said PLAG1 fragment gene encodes a protein comprising comprises at least one of the zinc fingers 1 to 7 represented by the sequences as represented in SEQ ID NOs: 117 to 123.

48. (Currently Amended): A macromolecule comprising a nucleic acid in isolated form, comprising a sequence encoding fusion of at least two of an oligonucleotide, a polynucleotide and a gene having a nucleotide sequence of at least one exon of the promoter region of a CTNNB1 gene ,or the complementary sequence or antisense versions of the nucleotide sequence which can be used to diagnose cells having a non-physiological proliferative capacity.

49. (Canceled)

50. (NEW): A macromolecule according to claim 48, wherein said nucleic acid is selected from the group consisting of a transcript corresponding to the nucleic acid, a cDNA corresponding to the nucleic acid, and a sense or antisense DNA corresponding to the nucleic acid.

51. (NEW): A macromolecule comprising a nucleic acid in isolated form comprising at least one exon of the CTNNB1 gene, which can be used to diagnose cells having a non-physiological proliferative capacity.

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52. (NEW): A macromolecule according to claim 51, wherein said nucleic acid is selected from the group consisting of a transcript corresponding to the nucleic acid, a cDNA corresponding to the nucleic acid, and a sense or antisense DNA corresponding to the nucleic acid.